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(Review Article)

Transforming Glucose Detection: The Emerging Role of Transition Metal Oxide Nanomaterials in Enzyme-Free Biosensors

Gayathri Jeevanandham[1*]

[1*]*Chemical Sciences Department and The Radical Research Center, Ariel University, Ariel, ISRAEL*

Abstract

The global rise in diabetes prevalence has intensified the demand for glucose monitoring technologies that are accurate, cost-effective, and stable. Although enzyme-based glucose sensors are widely used, they face significant limitations, including poor stability, temperature sensitivity, and high manufacturing costs. As a promising alternative, enzyme-free glucose sensors based on transition metal oxide (TMO) nanostructures such as NiO, Co_3O_4, CuO and ZnO offer intrinsic electrocatalytic activity, chemical robustness, and tunable physicochemical properties. This review examines recent advances in the design, synthesis, and application of TMO based nanomaterials for non-enzymatic glucose detection. We highlight how nanoengineering strategies including morphology control, doping, and composite formation enhance sensor performance. The sensors discussed demonstrate high sensitivity, low detection limits, rapid response times, and excellent selectivity in complex biological matrices. These advancements underscore the potential of TMO nanostructures to enable reliable, scalable, and wearable glucose biosensors for real-time diabetes monitoring.

Keywords: Co_3O_4, CuO, glucose biosensor, nanomaterials, NiO, non-enzymatic detection, transition metal oxide, ZnO.

1. Introduction

Diabetes, a pressing global health concern, is characterized as a metabolic disorder that disrupts the body's ability to regulate blood sugar levels effectively. The statistics provided by the International Diabetes Federation (IDF) are alarming, with over 400 million people currently living with diabetes worldwide, and this number is projected to rise to a 642 million by the year 2040[1]. This increase would represent 10.4% of the world's population, making diabetes the seventh-leading cause of mortality. However, the impact of diabetes extends far beyond the individual level; it also poses a substantial barrier to sustainable development and economic growth on a global scale [2]. The root causes of diabetes can be attributed to either inadequate production of insulin by the pancreas (Type 1 diabetes) or the body's diminished ability to effectively utilize the insulin it produces (Type 2 diabetes). This rising prevalence of hyperglycemia, or elevated blood glucose levels, underscores the urgency of addressing this global epidemic and the imperative need for comprehensive solutions to mitigate its impact on health and socioeconomic development [3-5].

In both Type 1 and Type 2 diabetes, the ability to externally administer insulin to patients has been a crucial advancement in managing the condition. Insulin therapy plays a pivotal role in regulating blood sugar levels, and discontinuing this treatment can have serious consequences for a patient's health. Prolonged high blood sugar levels can lead to significant damage to multiple organ systems, particularly impacting the kidneys, eyes, nerves, and blood vessels. To facilitate effective diabetes management, medical devices have become invaluable tools. Among these devices, blood sugar monitoring devices are prominently featured. In the realm of diabetes care, market leaders such as Abbott Laboratories have made substantial contributions to the development of these devices. Notably, continuous glucose monitoring (CGM) systems have emerged as ground-breaking innovations. Unlike traditional glucose monitors, CGM systems provide a more comprehensive understanding of glucose levels and trends. These systems enable 24-hour, real-time monitoring of interstitial glucose levels, offering both patients and healthcare providers invaluable insights into managing blood sugar levels more effectively. This technology represents a significant step forward in the quest for better diabetes management and improved patient outcomes.

[*]*Corresponding Author: e-mail: gayathrij@ariel.ac.il, Tel-+972559453299*
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The history of glucose sensing and monitoring has seen remarkable developments since its inception. The concept of glucose sensors was first introduced by Clark and Lyons in the year 1962[6], setting the foundation for subsequent advancements in this field. One of the pivotal milestones occurred in 1980 with the introduction of the glucose meter, marking a significant leap in self-monitoring of blood glucose levels. This medical device became instrumental in providing individuals with diabetes a means to determine the approximate concentration of glucose in their blood, enabling better control of their condition. In 1967, Updike and Hicks made a groundbreaking contribution by describing the electrochemical glucose meter. Their work focused on the immobilization of glucose oxidase (GOx) in a gel on an oxygen electrode, which facilitated the measurement of glucose concentrations in biological fluids. This innovative approach laid the groundwork for a multitude of methods and applications in the field of glucose level detection [7]. In recent years, electrochemical glucose detection techniques, particularly those based on direct glucose electro-oxidation, have gained widespread recognition. These methods offer several advantages, including high sensitivity, a low limit of detection, promising response times, and cost-effectiveness.

This recognition underscores the growing importance of electrochemical methods in advancing glucose monitoring technologies, further enhancing our ability to manage and understand this critical aspect of diabetes care. In the realm of electrochemical sensors, they are typically categorized into two primary divisions: enzymatic sensors and non-enzymatic sensors. Enzymatic sensors have proven to be highly effective in detecting specific substances due to the selectivity of enzymes. However, they do come with a set of challenges. One significant drawback is the intricate process of immobilizing enzymes onto sensor surfaces, which can be both time-consuming and technically demanding. These sensors are also susceptible to variations in environmental conditions, which can affect their accuracy and reliability. Moreover, they may exhibit sensitivity issues, and long-term functional stability can be a concern. Lastly, the fabrication of enzymatic sensors can often be cost-prohibitive, making them less accessible for widespread use. These limitations have prompted ongoing research into non-enzymatic sensors, which aim to address some of these challenges and provide more versatile and cost-effective solutions for various applications [8-11].

2. Evolution of Glucose Sensor Technology

Over the past several decades, glucose sensor technology has undergone a remarkable transformation, evolving through four major generations. These advancements were motivated primarily by the clinical need for highly sensitive, selective, stable, and real-time glucose monitoring systems, especially for diabetic care. Each generation introduced innovations that addressed the limitations of its predecessors, culminating in the emergence of enzyme-free electrochemical glucose sensors.

2.1 First generation: oxygen-dependent enzymatic sensors: The first-generation glucose sensors, pioneered by Clark and Lyons in the 1960s, relied on the enzymatic oxidation of glucose using glucose oxidase (GOx). In this design, molecular oxygen served as the natural electron acceptor, and the electrochemical detection was based on measuring the hydrogen peroxide (H_2O_2) produced during the reaction. The enzymatic reaction can be represented as:

$$\boldsymbol{Glucose + O_2 \xrightarrow{GOx} Gluconicacid + H_2O_2} \quad (1)$$

The subsequent electrochemical reaction at the electrode is:

$$H_2O_2 \rightarrow 2H^+ + 2e^- + O_2 \quad (2)$$

Although simple and direct, these sensors were highly dependent on ambient oxygen concentration and suffered from interference by endogenous electroactive substances such as uric acid, ascorbic acid, and acetaminophen.

2.2 Second generation: mediator-based enzymatic sensors: To overcome oxygen dependency, second-generation sensors introduced artificial redox mediators such as ferrocene, ferricyanide, and quinones that shuttle electrons from the reduced enzyme to the electrode surface, bypassing the need for oxygen. The core reactions are:

$$\text{Glucose} + \text{GOx (FAD)} \rightarrow \text{Gluconolactone} + \text{GOx (FADH}_2\text{)} \quad (3)$$

$$\text{GOx (FADH}_2\text{)} + 2\text{M(ox)} \rightarrow \text{GOx (FAD)} + 2\text{M(red)} \quad (4)$$

$$2\text{M(red)} \rightarrow 2\text{M(ox)} + 2e^- \quad (5)$$

This approach enabled glucose detection in low-oxygen environments and allowed operation at lower potentials, thereby improving selectivity. However, challenges such as mediator leakage, toxicity, and long-term instability remained.

2.3 Third generation: direct electron transfer sensors: Third-generation sensors aimed to achieve direct electron transfer (DET) between the redox center of GOx and the electrode, eliminating the need for mediators. This required advanced electrode materials like carbon nanotubes, gold nanoparticles, or conductive polymers to bridge the enzymes deeply buried active site. The reactions are:

$$\text{Glucose} + \text{GOx (FAD)} \rightarrow \text{Gluconolactone} + \text{GOx (FADH}_2\text{)} \quad (6)$$

$$GOx\ (FADH_2) \rightarrow GOx\ (FAD) + 2H^+ + 2e^- \quad (7)$$

DET sensors offer superior specificity and avoid mediator-related drawbacks but are often limited by inefficient electron tunneling through the protein matrix.

2.4 Fourth generation: enzyme-free electrochemical sensors: The latest generation relies on enzyme-free electrochemical sensing, utilizing non-biological catalysts typically transition metals, metal oxides, sulfides, or carbon-based nanomaterials—to directly catalyze glucose oxidation. In alkaline media, the reaction can be summarized as:

$$Glucose + OH^- \rightarrow Gluconolactone + H_2O + 2e^- \quad (8)$$

In the pursuit of more advanced glucose sensing technologies, the third-generation sensors, while an improvement, continued to grapple with certain limitations associated with enzyme-based systems. These limitations encompassed factors such as enzyme activity being susceptible to variations in temperature, humidity, and interference from external sources [12-14]. To address these shortcomings, non-enzymatic glucose sensors have emerged as a promising fourth-generation solution for analytical applications. These sensors offer a range of advantages, including cost-effectiveness, heightened stability, rapid response times, extremely low detection limits, and exceptional sensitivity. Notably, extensive research has been dedicated to developing non-enzymatic glucose sensors utilizing various nanomaterials, particularly those composed of metals such as platinum (Pt), palladium (Pd), gold (Au), and their alloys like Pt-Ru, Pt-Pb, and Pt-Au, among others.

While noble metal-based materials, such as Pd-single-walled carbon nanotubes (SWCNT), Pt-carbon nanotubes (CNT), multi-walled carbon nanotubes (MWCNT) with RuO2, and Au-Pt alloys, exhibit robust electrocatalytic activity, they do come with limitations stemming from their relatively high cost and susceptibility to chemisorbed intermediates and chloride ions. As a result, the scientific community has increasingly turned its attention to transition metals, including tungsten (W), manganese (Mn), zinc (Zn), iron (Fe), cobalt (Co), nickel (Ni), and copper (Cu), as well as transition metal oxides like copper oxide (CuO), manganese trioxide (Mn2O3), cobalt oxide (Co3O4), nickel oxide (NiO), tungsten oxide (WO3), and ruthenium oxide (RuO2). These materials are being recognized for their cost-effectiveness as electrocatalysts in the development of non-enzymatic electrochemical glucose sensors. Importantly, it should be noted that the properties of these non-enzymatic sensors, including sensitivity, selectivity, response times, and stability, heavily hinge on the choice of electrode material and its specific nanostructure, underlining the importance of material selection in optimizing glucose monitoring technology.

3. Utilizing Metallic Redox Centers for Direct Glucose Oxidation

Electrocatalytic processes are primarily governed by the adsorption of reactant molecules onto active sites located on the electrode surface. This adsorption mechanism is influenced by several factors, including the favorable electronic states of the redox center, the presence of unfilled d-orbitals in transition metal centers, or the existence of defects in catalysts based on non-metals. When reactants adsorb onto these active sites, they undergo bond-breaking and intermediate formation. As the oxidation state of the redox center changes, the interaction between the reaction product and the electrode weakens, ultimately leading to the desorption of the product from the electrode surface. This dynamic process, characterized by the adsorption and subsequent desorption of reactants on the electrode, is commonly referred to as the chemisorption model [15-16].

In the context of glucose oxidation driven by chemisorption, as a glucose molecule approaches the electrode, there is an intensified chemical interaction between the carbon atom at position C-1 and its hydrogen atom with the electrode surface. This heightened interaction facilitates the dehydrogenation of C-1 and its subsequent adsorption onto the electrode surface. Subsequently, the electro-oxidation of these adsorbed species occurs, leading to the formation of glucono-dlactone. This compound further undergoes oxidation, resulting in the production of gluconic acid through distinct reaction pathways, which may vary depending on the pH conditions [17-21]. This intricate process underscores the complex and fascinating mechanisms underlying electrocatalytic glucose oxidation. The chemisorption process crucial to the glucose oxidation is illustrated. Initially, glucose molecules adhere to the metal electrode surface through a coordinated series of hydrogen abstraction and the chemisorption of a reactive intermediate. It is only after this initial step that the subsequent oxidation of glucose occurs/ the concept of the incipient hydrous oxide/adatom mediator model. This model postulates the existence of a reactive hydrous oxide layer (OH ads) on the electrode surface, which is believed to expedite the rapid electro-oxidation of glucose, ultimately resulting in the formation of glucono-d-lactone. This representation is adapted from the referenced source, providing valuable insights into the intricate mechanisms governing glucose oxidation at the electrode surface [15].

Moreover, during electrocatalysis, the formation of surface-bound reactive hydroxide species (OH ads) plays a pivotal role in influencing the redox reactions of small organic molecules. In this complex electrocatalytic process, the Incipient Hydrous Oxide/Adatom Mediator (IHOAM) model, as proposed by Burke and his colleagues, offers valuable insights. This model effectively complements the previously established chemisorption-based electrocatalysis model16. According to the IHOAM framework, the presence of a premonolayer of reactive OH ads on metal sites with low lattice coordination numbers mediates a variety of redox reactions. This is underscored by the correlation between the onset potential of these redox reactions and the potential at which OH ads formation takes place [17-20]. Additional research focusing on glucose oxidation, utilizing

diverse metal electrodes, has also substantiated the role of reactive OH ads in the process [21].

It is worth noting that the chemisorption and IHOAM models predominantly apply to noble metal electrodes like Pt and Au. Consequently, these explanations may not be universally applicable to a broader spectrum of materials, particularly transition metals or metal oxide-based electrodes. Instead, a more comprehensive understanding of glucose oxidation on such materials, including Ni, Cu, and Co [22], can be obtained by examining the redox reactions taking place at the transition metal centers. Under an anodic bias, the metal oxide layer with a lower oxidation state, often referred to as the lower oxide, undergoes oxidation, transitioning into the metal oxide with a higher oxidation state known as the higher oxide. This higher oxide exhibits adequate oxidative potential to generate surface-bound OH ads radicals, which are highly proficient in oxidizing organic reactants in close proximity to the electrode's surface. An essential initial step in glucose oxidation entails the abstraction of the hydrogen atom at the C-1 position [23].

Subsequently, as the electrocatalytic process unfolds, there is a further oxidation of reaction intermediates, culminating in the production of glucono-d-lactone. The precise mechanisms driving these reactions, while not yet entirely elucidated, are believed to involve factors such as surface hydroxyl radicals, hydroxide ions, or solvent molecules present with in the reaction solution. The hydrogen abstraction step in this sequence is often regarded as the rate-determining factor, akin to noble metals. However, the actual adsorption process of reactants on these materials remains enigmatic or is thought to engage unconventional reaction pathways [23-24]. In the realm of research within this field, most investigations employ voltametric techniques, particularly amperometry methods, to explore the direct oxidation of glucose on electrodes. The conditions for glucose oxidation reactions typically lean towards neutrality or alkalinity, with acidity being a rare choice. This preference can be attributed to several factors, including the advantageous formation of reactive OH ads species in alkaline environments, the susceptibility of transition metal and metal oxide-based electrode materials to instability in acidic settings, and the prevalence of easily oxidizable β-glucopyranoses at higher pH levels, a phenomenon attributed to mutarotation. The glucose concentration, allowing for real-time glucose monitoring. The current response can be quantified, providing accurate and sensitive measurements of glucose levels.

This review highlights the advancements in non-enzymatic glucose sensors based on transition metal oxide (TMO) nanomaterials. By categorizing sensors according to MOS types and presenting their performance metrics through tables and visual figures, the paper provides a comprehensive overview of recent developments. TMOs such as NiO,CuO,Co_3O_4, and MnO_2 offer notable advantages due to their electrocatalytic activity, structural flexibility, and chemical stability. Nanostructuring and hybridization techniques have further enhanced their sensitivity and durability. Despite current challenges like selectivity and large-scale integration, future innovations in material design and AI-driven analytics promise to drive the development of intelligent, real-time glucose monitoring systems with significant impact on healthcare and diagnostics

A conventional way to plan a manuscript is to construct an outline. An outline has two interacting purposes. One is to shape the technical information in logical order and other is to help in organizing and thinking about paper. It should be flexible. The main text should be divided into several sections and subsection. There should be continuity in the presentation. The style of sections and subsection are generally given in the guidelines of the journal. If nothing is available, it is preferable to see the previous issue of the journal concerned. The complex mathematical derivation should be placed in the appendix of the paper, which is placed at end of the paper.

4. Transition Metal Oxides for Glucose Detection

4.1 NiO-based non-enzymatic glucose sensors: Nickel oxide (NiO) is a p-type semiconductor with a wide bandgap (3.6–4.0 eV) and notable redox activity through the Ni^{2+}/Ni^{3+} couple. Its non-toxicity, abundance, cost-effectiveness, and high theoretical specific capacitance (~2584 F/g) make it an attractive material for non-enzymatic glucose sensors.

4.1.1 Sensing mechanism: NiO facilitates glucose detection via surface-catalyzed electrochemical oxidation, converting glucose to gluconolactone and generating an electron current proportional to glucose concentration:

$$NiO + OH^- \rightarrow NiOOH + e^- \quad (9)$$

$$\boldsymbol{Ni(OH)_2 + OH^- \leftrightarrow NiOOH + H_2O + e^-} \quad (10)$$

$$NiOOH + \text{glucose} \rightarrow Ni(OH)_2 + \text{gluconolactone} \quad (11)$$

4.1.2 Literature review and performance: Lu et al. [25] (2013) introduced porous Ni foam for glucose sensing, achieving a detection limit of 2.2 mM, linear range 0.05–7.35 mM, and sensitivity ~500 μA/mM·cm².Ahmed A. Ibrahim et al. fabricated NiO nanosheets via hydrothermal synthesis for mono- and disaccharide detection. Yudong Zhao et al. developed $Ni(OH)_2$ nanosheets on Ni foam by direct precipitation. The sensor showed high sensitivity (1097–1130 μA/mM·cm²), low detection limit (1 μM), and fast response (<2 s) at 0.51 V in 0.2 M NaOH. Chung-Wei Kung et al[26]. deposited $Ni(OH)_2$ nanoparticles on nickel foam via cyclic voltammetry. The resulting electrode exhibited excellent electrocatalytic activity with a sensitivity of 1950.3 μA/mM·cm², detection limit 0.16 μM, linear range 0.6–6.0 mM, at 0.45 V. Ying Muet al. improved NiO-modified carbon paste electrodes by scanning to 1.2 V, enhancing conversion to $Ni(OH)_2$ and NiOOH. The sensor responded within 5 s, with sensitivities of 66 and 55.9 μA/mM across 1–110 mM glucose, and a detection limit of 0.16 μM. It demonstrated high selectivity against ascorbic and uric acids at 0.7 V in 0.5 M NaOH [27].

Shu-Hui Yeh et al. enhanced sensor performance by incorporating graphene oxide–polyvinyl alcohol composites with electroplated nickel–cobalt catalysts, improving sensitivity and selectivity for glucose and insulin detection. Houqiang Chen et al. developed a flexible enzyme-free glucose sensor using multilayer porous laser-induced graphene (LIG) with electrochemically deposited Ni nanoparticles. The sensor showed high sensitivity (2040 μA/mM·cm²), a wide detection range (0.50 μM–1666 μM), excellent stability, and accurate glucose detection in human serum.

4.2 Co_3O_4-Based non-enzymatic glucose sensors: Tricobalt tetroxide (Co_3O_4) is a promising material for glucose sensors due to its excellent catalytic activity, electrical conductivity, and chemical stability. This section reviews Co_3O_4 synthesis methods, sensing mechanisms, electrochemical performance, and structural advances.

4.2.1 Sensing mechanisms: Co_3O_4 enables glucose sensing primarily via non-enzymatic catalytic oxidation, involving redox transitions between Co^{2+}/Co^{3+} and Co^{3+}/Co^{4+}:

$$Co_3O_4 + OH^- + H_2O \leftrightarrow 3CoOOH + e^- \quad (12)$$

$$CoOOH + OH^- \leftrightarrow CoO_2 + H_2O + e^- \quad (13)$$

$$2CoO_2 + glucose \rightarrow 2CoOOH + gluconolactone \quad (14)$$

4.2.2 Morphological and structural advances: Yu Ding[28] et al. fabricated uniform Co_3O_4 nanofibers (~105 nm diameter) via electrospinning and calcination, drop-cast on glassy carbon electrodes (GCE) with Nafion binder. Cyclic voltammetry in alkaline media revealed two redox peak pairs linked to $Co_3O_4 \leftrightarrow CoOOH$ and $CoOOH \leftrightarrow CoO_2$ transitions. Glucose addition increased current notably at the $CoOOH \rightarrow CoO_2$ peaks. The sensor showed a fast response (<7 s), sensitivity of 36.25 μA mM^{-1} cm^{-2}, detection limit 0.97 μM, and good reproducibility. However, selectivity was poor against ascorbic acid (AA) and uric acid (UA), which caused higher interference currents.

Q. Dong [29] et al. prepared N-doped hollow Co_3O_4 nanofibers (~294 nm diameter) via core-sheath electrospinning. CV results and sensing mechanism resembled prior findings. Electron transfer numbers were 1.0 and 0.8 for $CoOOH \rightarrow CoO_2$ and $Co_3O_4 \rightarrow CoOOH$, respectively. The sensor responded rapidly (5 s), had sensitivity 87.67 μA mM^{-1} cm^{-2}, detection limit 0.38 μM, and acceptable selectivity. It successfully measured glucose in human serum (~6.50 mM), consistent with commercial sensors. L. Kang synthesized porous Co_3O_4 nanowires (200–300 nm diameter) by hydrothermal method and calcination. The porous structure increased active sites and electrolyte access. The sensor exhibited sensitivity of 300.8 μA mM^{-1} cm^{-2}, detection limit 5 μM, and response time <5 s at 0.6 V in 0.3 M NaOH, with good selectivity against UA, dopamine, and AA. However, current increments were limited between 5 μM and 0.57 mM glucose.

M. Zheng [30] et al. developed ordered porous Co_3O_4 materials with varying pore sizes (5, 20, 70 nm) via hard-template synthesis using KIT-6 and SiO_2 templates. Despite Co_3O_4-70 having the lowest BET surface area (32.6 m^2/g), it showed superior sensitivity and lowest detection limit (0.025 μM) in 0.1 M NaOH at 0.6 V. The larger pores likely enhanced electrolyte penetration and glucose transport. The sensor demonstrated good repeatability and selectivity against AA, UA, dopamine, and KCl, though slight interference was noted.

4.3 CuO-Based non-enzymatic glucose sensors:

4.3.1 Sensing mechanisms: CuO is an attractive substrate for non-enzymatic glucose (NEG) sensors due to its high electrochemical activity, low cost, non-toxicity, and ease of modification. Glucose oxidation on CuO electrodes in alkaline media proceeds via Cu(II)/Cu(III) redox pairs through these steps:

$$CuO + OH^- \rightarrow Cu(OH)_2 + e^- \quad (15)$$

$$\boldsymbol{CoOOH + OH^- \leftrightarrow CoO_2 + H_2O + e^-} \quad (16)$$

$$CuOOH + glucose \rightarrow Cu(OH)_2 + gluconolactone \quad (17)$$

4.3.2 Morphological and structural advances: Early studies demonstrated carbohydrate oxidation on copper oxide-coated electrodes in alkaline potassium hydroxide solutions using potential sweep methods. Later, Cu(II)-modified glassy carbon electrodes detected mono- and disaccharides electrochemically in alkaline media, employing hydroxyl radical-activated metal oxide sites (CuO•OH). Cu2O-modified electrodes showed catalytic activity, with CuO formed in situ as the active species, although carbohydrate differentiation remained challenging at +0.55 V[31-32].You et al. [33]showed that higher CuO/$Cu(OH)_2$ content (4.5%) enhanced glucose electrooxidation sensitivity compared to 2.6% copper oxide/hydroxide nanoparticles. Batchelor–McAuley et al.[34]confirmed CuO nanoparticles' critical role in glucose oxidation over metal-free carbon nanotubes, highlighting their catalytic importance. The sensing mechanism involves hydroxyl ion adsorption forming CuxOOH intermediates, catalyzing carbohydrate oxidation at applied potentials in alkaline media. Various materials have been used to boost sensor sensitivity by enhancing electron transfer, including carbon cloth, multi-walled carbon nanotubes, graphene and derivatives, Vulcan XC72, and metal-organic frameworks (MOFs) Strategies such as increasing copper oxide surface area and combining conducting polypyrrole with reduced graphene oxide further improve performance.

Inkjet printing CuO on Si/Ag substrates, Ag-patterned surfaces and Au films enable portable, test-strip glucose sensors. Mesoporous CuO immobilized on base-leached MFI zeolite (10–30 nm pores) enhances glucose sensing in alkaline [35-37]. Ce-MOF/CuO nanoparticle composites exhibit ultra-sensitivity (2058.5 μA mM^{-1} cm^{-2}) with a detection limit as low as 2 nM, attributed to Cu(II)/Cu(III) oxidation catalyzing glucose oxidation and facilitated

electron transfer. Electron transfer resistances (Rct) support Ce-MOF's role in enhancing sensor performance.

4.4 ZnO-based non-enzymatic glucose sensors: Zinc oxide (ZnO), a II–VI semiconductor with a wide bandgap (3.37 eV), exhibits high electron mobility, chemical stability, electrochemical activity, and a high isoelectric point, making it highly suitable for biosensing applications. These attributes support effective enzyme adsorption and biocompatibility, although ZnO has only recently been explored for non-enzymatic glucose sensing. A significant breakthrough was reported by Dar et al. [38], who fabricated a ZnO nanorod-modified glassy carbon electrode (GCE) via hydrothermal synthesis. The sensor demonstrated excellent performance using I–V measurements, achieving a sensitivity of 5.601 mA mM^{-1} cm^{-2}, a detection limit of 0.5 mM, and a fast response time of 10 s. The proposed sensing mechanism involves the adsorption of O_2 at the ZnO surface, electron transfer to form reactive oxygen species, and glucose oxidation to glucono-δ-lactone and gluconic acid.

Further advances have focused on enhancing performance through hybrid structures. So Yoon [39] et al. developed a hierarchical Cu/CuO/ZnO nanostructure combining CuO nano leaves and ZnO nanorods, significantly boosting electrocatalytic activity via synergistic interactions. This configuration exhibited high sensitivity (609.8 μA mM^{-1} cm^{-2}), a low detection limit (0.3 mM), and a rapid response (3 s) with excellent selectivity. Singh [40] et al. synthesized highly crystalline ZnO nanoparticles via a solution-based method and modified a gold electrode, achieving a sensitivity of 38.13 μA mM^{-1} cm^{-2} and a response time under 5 s. Their ZnO–CuO hierarchical nanocomposite reached 3066.4 μA mM^{-1} cm^{-2} sensitivity, a detection limit of 0.21 mM, and demonstrated high stability and reproducibility in real serum analysis. Despite these successes, ZnO-based sensors often require relatively high operating potentials, increasing susceptibility to interference from species like ascorbic acid and uric acid. Ahmad [41] et al. addressed this by synthesizing vertically aligned ZnO nanorods on FTO substrates and coating them with CuO. The resulting CuO–ZnO hybrid sensor offered enhanced surface area, efficient electron transport, and a low detection limit of 0.40 μM, with a sensitivity of 2961.7 μA mM^{-1} cm^{-2} and excellent reproducibility in serum samples. In another study, Liu [42] et al. developed mesoporous ZnO–NiO nanosheet architectures via annealing zinc–nickel hydroxycarbonate precursors. These electrodes showed a detection limit of 0.5 mM, a sensitivity of 120.5 μA mM^{-1} cm^{-2}, and a linear range up to 6.4 mM. Their porous structure and synergistic metal oxide interactions contributed to fast response times (<3 s) and enhanced sensing efficiency.

5. Mechanism of Non-Enzymatic Glucose Sensing

Non-enzymatic glucose sensing relies on the electrochemical oxidation of glucose molecules directly at the electrode surface without the involvement of enzymes. Transition metal oxides (TMOs) serve as catalysts in this process by facilitating the oxidation of glucose into gluconolactone, while simultaneously reducing oxygen to produce hydroxide ions (OH^-) at the electrode surface. This electrochemical reaction typically occurs in an alkaline solution, where glucose oxidation proceeds as follows Glucose Oxidation: In an alkaline medium, glucose undergoes oxidation at the surface of the TMO electrode. The oxidation process involves the transfer of electrons from glucose to the electrode, producing gluconolactone and hydroxide ions (OH^-). Electrocatalytic Activity: The transition metal oxide surfaces (such as NiO, Co_3O_4, CuO, and MnO_2) provide active sites for the glucose oxidation reaction. These surfaces can accept and donate electrons, facilitating the electron transfer necessary for glucose oxidation. The electrocatalytic activity of TMOs is crucial for the rapid and efficient oxidation of glucose at lower potentials, which reduces interference from other species in complex biological samples, such as serum or sweat.

TMO Electrochemical Properties: TMOs are often used because they possess unique electrochemical characteristics, including high catalytic efficiency, stability, and excellent conductivity. The surface area and morphology of TMOs significantly impact their catalytic activity, as higher surface area provides more active sites for glucose oxidation. Nanostructured TMOs, such as nanowires or nanosheets, are particularly effective due to their enhanced conductivity and larger surface-to-volume ratios compared to bulk materials. Electrochemical Detection: The glucose oxidation reaction produces electrons, which are detected by electrochemical methods such as amperometry, cyclic voltammetry (CV), or chronoamperometry. In amperometric sensing, the current generated by the oxidation of glucose is directly proportional to the glucose concentration, allowing for real-time glucose monitoring. The current response can be quantified, providing accurate and sensitive measurements of glucose levels.

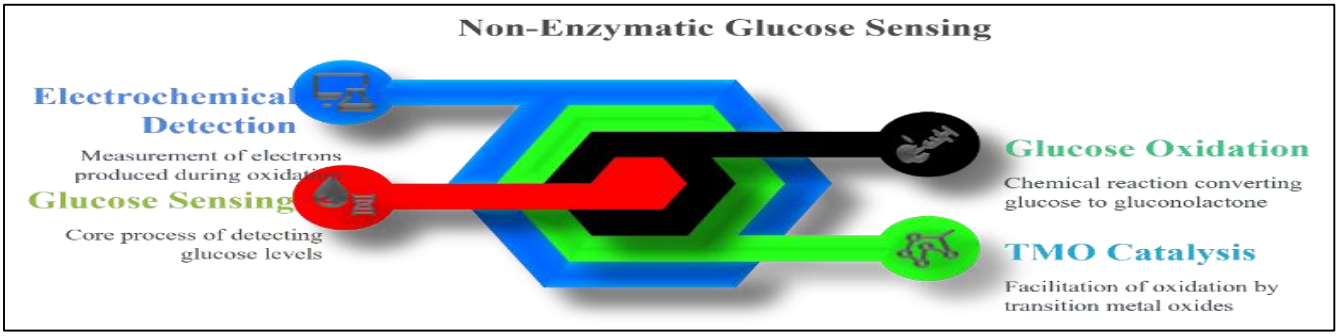

Figure 1. Schematic diagram of non-enzymatic glucose sensing

5.1 Glucose monitoring methods: Effective diabetes management hinges on the timely and accurate monitoring of blood glucose levels, which plays a vital role in preventing complications associated with the disease. Traditional glucose monitoring systems, although widely used, are often invasive and may not be suitable for continuous or frequent usage. As a result, there has been a significant push in research toward developing more user-friendly, non-invasive glucose monitoring technologies. Based on their operational mechanism and degree of invasiveness, glucose monitoring systems are broadly categorized into three types:

5.1.1 Invasive glucose monitoring systems: These conventional devices typically use electrochemical sensing techniques and require skin penetration using a lancet to draw blood. The blood sample is then analyzed on a test strip to determine glucose levels. This method offers rapid and straightforward readings without the need for trained personnel. However, repeated finger-pricking can lead to discomfort, skin irritation, or infections, thereby reducing patient adherence.

5.1.2 Minimally invasive monitoring systems: These systems enable continuous monitoring of glucose in the interstitial fluid through subcutaneously implanted sensors. Most of these devices operate via enzymatic reactions involving glucose oxidase (GOx), which catalyzes glucose detection in real-time) Despite their advantage of tracking glucose fluctuations throughout the day, prolonged use may result in tissue irritation or damage at the insertion site. Nevertheless, they offer better glycemic control by allowing timely therapeutic interventions and reducing the likelihood of diabetes-related complications.

5.1.3 Non-invasive glucose monitoring systems: Low compliance with invasive and minimally invasive devices has fueled the exploration of non-invasive technologies. These systems aim to measure glucose without breaching the skin, offering a pain-free and more convenient alternative. Techniques such as near-infrared (NIR), mid-infrared (MIR), Raman spectroscopy, impedance spectroscopy, and ultrasound-based methods are currently under investigation. Although a few optical-based devices have reached the development stage, many still face challenges related to measurement accuracy and consistency. Table 1 shows a comparison of ZnO-, CuO-, NiO-, and Co_3O_4-based non-enzymatic glucose sensors.

Table 1. Comparison of ZnO-, CuO-, NiO-, and Co_3O_4-based non-enzymatic glucose sensors

Material	Morphology/structure	Sensitivity ($\mu A \cdot mM^{-1} \cdot cm^{-2}$)	Detection limit (LOD)	Linear range (mM)	Response time	Key advantages	Refs
NiO	Nanosheets on Ni foam	1130, 1097	1 µM	0.1–2.5 / 2–40	<2 s	High surface area, fast kinetics	[2]
	Ni $(OH)_2$ NPs on Ni foam	1950.3	0.16 µM	0.6–6.0	<2 s	Simple CV deposition method	[3]
	Modified carbon paste	66, 55.9 $mA \cdot mM^{-1}$	0.16 µM	1–10 / 1–110	5 s	Good selectivity vs AA/UA	[4]
Co_3O_4	Nanofibers	36.25 $mA \cdot mM^{-1}$	0.97 µM	0–2.04	<7 s	OH^- activation, reversible peaks	[5]
	N-doped hollow nanofibers	87.67	0.38 µM	NR	<5 s	High e^- transfer rate	[6]
	Porous nanowires	300.8	5 µM	0.005–0.57	<5 s	Excellent selectivity	[7]
CuO	MOF-derived nanorods	1523.5	NR	NR	NR	High catalytic area	[8]
	LIG with Ni NPs	2040	0.29 µM	0.0005–1.666	Flexible	Excellent mechanical durability	[9]
ZnO	Nanorods (GCE)	5601	0.5 mM	NR	10 s	Simple hydrothermal synthesis	[10]
	CuO–ZnO hybrid	2961.7	0.40 µM	up to 8.45	<2 s	High surface area, real serum test	[11]
	ZnO-NiO mesoporous sheets	120.5	0.5 mM	0.5–6.4	<3 s	Synergistic interaction	[12]

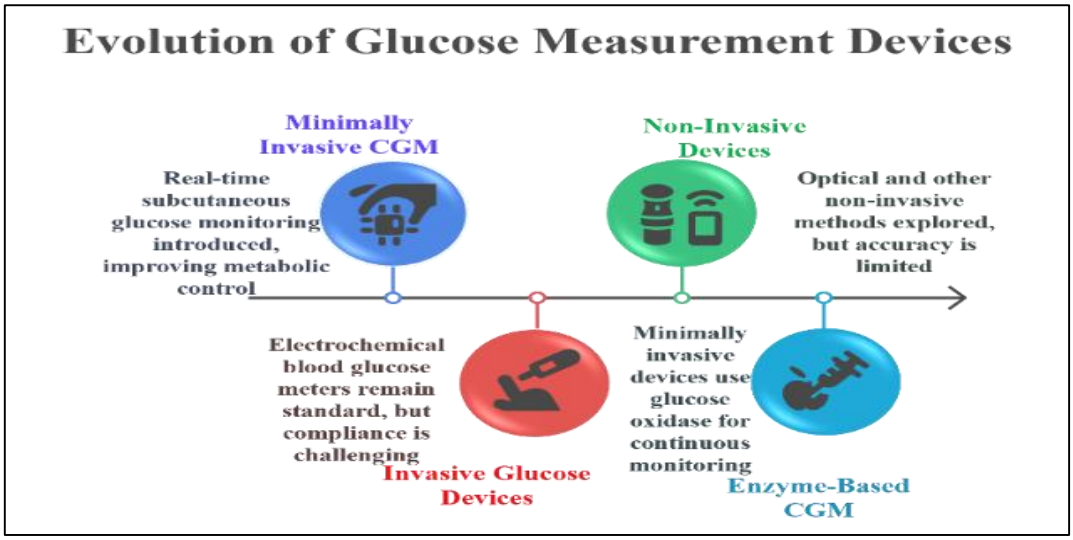

Figure 2. Represents a visual overview of various glucose monitoring techniques

6. Prospects for Non-Enzymatic Glucose Sensing

Non-enzymatic sensors have garnered substantial interest as an intriguing alternative to address the inherent limitations of enzyme sensors. They hold the potential to resolve issues related to stability and the complex, unreliable processes involved in mass-producing enzyme sensors. Consequently, an increasing number of research publications are emerging in this field. Over the past decade, rapid advancements in nanotechnology and nanomaterials have greatly contributed to the sophistication and diversification of non-enzymatic glucose sensing. One remarkable achievement in this area has been the significant progress in the clinical applications of enzyme-free systems, particularly those based on nanoporous electrodes. Researchers have demonstrated that by finely tuning parameters such as pore size, nanoporous film thickness, and protective coatings, non-enzymatic glucose probes can effectively operate in undiluted human serum, plasma, and whole blood, while also mitigating interferences from various electro inactive and electroactive molecules. Additionally, a reliable fabrication protocol for these non-enzymatic glucose probes has been established, enabling their operation for over 30 days in undiluted whole blood following a thorough sterilization process using autoclaving a method that would be detrimental to enzyme-based electrodes.

Furthermore, the potential for implantable probes for continuous glucose monitoring is on the horizon. The chemical processes involved in nano porous film fabrication may also facilitate the mass production of disposable non-enzymatic glucose strips. Nevertheless, non-enzymatic sensors have not yet surpassed enzyme sensors. In terms of commercialization, there is still a long road ahead. Many studies have heavily leaned toward material-centric approaches, often based on various combinations of substances and structural engineering. The testing conditions employed are often impractical, underscoring the functional limitations of the proposed systems or materials from a practical glucose sensing standpoint. Moving forward, research in this field must explore novel materials that hold the potential to bring about breakthroughs in electrode and protective film design. To achieve practical use and mass production, an even greater effort is required to delve into the sensing mechanisms and address the challenges hindering reliable operation in clinical samples. The next phase, following laboratory-scale studies with new materials, should focus on the professional development of mature technology, offering effective solutions for the commercialization of non-enzymatic sensors.

7. Conclusions

The emergence of transition metal oxide (TMO) nanostructures as core materials for enzyme-free glucose sensors has marked a paradigm shift in biosensor technology. Traditional enzymatic sensors, while effective in controlled environments, suffer from inherent limitations such as poor long-term stability, high cost of enzyme immobilization, temperature sensitivity, and operational complexity. In contrast, TMO-based non-enzymatic sensors exhibit several advantages including high electrocatalytic activity, cost-effectiveness, environmental robustness, and tunability via nano structuring. This review has explored the recent developments in TMO-based glucose sensors, specifically focusing on nickel oxide (NiO), cobalt oxide (Co_3O_4), copper oxide (CuO), and zinc oxide (ZnO) nanostructures. Each of these materials offers unique electrochemical and structural advantages. For instance, NiO's excellent redox behavior and biocompatibility, Co_3O_4's multi-valent oxidation states and high conductivity, CuO's strong catalytic ability and affordability, and ZnO's large bandgap and high isoelectric point contribute to their efficacy as sensing materials.

Furthermore, their performance is enhanced when engineered into nanoscale morphologies such as nanowires, nanosheets, hollow spheres, and hierarchical structures. These configurations increase the number of active sites, improve electron transport, and provide superior interaction with glucose molecules. A notable trend across recent literature is the hybridization of TMOs with conductive or catalytic supports like graphene, carbon nanotubes, noble metal nanoparticles, or conductive polymers. These hybrid

materials synergistically combine the high surface area and conductivity of supports with the catalytic functionality of TMOs, leading to sensors with lower detection limits, wider linear ranges, and greater selectivity against interferents. Additionally, compositing with metal-organic frameworks (MOFs), doping with heteroatoms, and surface treatments have shown promise in further tuning sensor performance. Despite these advances, challenges remain. One of the most pressing issues is selectivity in complex biological fluids. Electroactive species such as ascorbic acid, uric acid, and dopamine can produce interfering signals, especially at higher operating potentials. This calls for further innovations in surface chemistry and material design to develop more selective catalytic sites. Another bottleneck is scalability. While many sensors demonstrate excellent performance at the laboratory scale, their reproducibility and integration into commercial platforms particularly wearable devices remain underexplored. Furthermore, mechanical flexibility and physiological compatibility are critical considerations for next-generation wearable and implantable glucose sensors. The integration of TMO nanomaterials into soft, stretchable substrates without compromising their electrochemical performance is a field in need of more research. Future efforts should also focus on developing non-invasive sensing modalities, such as those based on interstitial fluid, sweat, or saliva, which require sensors to operate reliably in low-glucose-concentration and high-interference environments.

The future trajectory of this field lies in multidisciplinary integration. Coupling materials science innovations with microelectronics, data analytics, and artificial intelligence could lead to intelligent, closed-loop glucose monitoring systems. For instance, real-time data from wearable TMO-based sensors could be processed through AI algorithms to detect trends, predict glycemic events, and provide actionable feedback for diabetes management. Additionally, advances in flexible electronics and energy harvesting technologies could further enable the development of autonomous glucose monitoring patches or smart textiles. Importantly, regulatory and clinical validation pathways must be established early in the development cycle. To ensure safe and effective translation of TMO-based glucose sensors from bench to bedside, collaboration with clinicians, regulatory agencies, and manufacturers is essential. Standardized protocols for sensor testing such as reproducibility, biocompatibility, response time, and interference testing must be adopted to enable objective performance comparisons and inform iterative design improvements.

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Biographical notes

Dr. J Gayathri Guru Prasad received her Ph.D. in Chemistry from the SRM Institute of Science and Technology, India. She is currently a Postdoctoral Researcher at The Radical Research Center, Ariel University, Israel. Her research interests include electrochemical sensors, nanomaterials, biomedical diagnostics, catalysis, Fenton-like reactions, and electron exchange columns. Dr. Jeevanandham is actively engaged in developing advanced materials and novel analytical techniques for next-generation diagnostic and environmental applications.